Treatment of Behavioral Disturbances of Dementia

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Psychiatry in Primary Care:
Meeting the Needs of Senior Patients
June 7, 2019
Objectives

1. Describe the epidemiology of BPSD

2. Discuss the assessment of individuals with BPSD.

3. Compare and contrast the evidence based management of individuals with BPSD.
Disclosures

• There are no FDA-approved medications for the treatment of behavioral and psychological symptoms of dementia and hence all medications discussed today are “off label” in their use.

• I have no conflicts of interest to disclose for this presentation.

• Acknowledgements: Raj Tampi, MD
Epidemiology of BPSD
Behavioral and Psychological Symptoms of Dementia

- These are a heterogeneous range of psychological reactions, psychiatric symptoms and behaviors that may be unsafe, disruptive and impair the care of the patient in a given environment.

- Very common
  - 65% patients with dementia in the community
  - 90% patients with dementia in nursing home setting

- Psychomotor agitation is the most persistent. (And most variably defined.)

Barucha et al, CNS Spectrum, 2002
Tampi et al, Clinical Geriatrics, 2011
## Classification

<table>
<thead>
<tr>
<th>Phenomenological</th>
<th>Etiologic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Affective:</strong> depression, anxiety, agitation, apathy, mania</td>
<td><strong>1. Primary:</strong> not due to any known etiology</td>
</tr>
<tr>
<td><strong>2. Psychotic:</strong> delusions, hallucinations</td>
<td><strong>2. Secondary:</strong> due to an underlying medical or psychiatric disorder</td>
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<tr>
<td><strong>3. Sleep-Wake cycle disturbance</strong></td>
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<tr>
<td><strong>4. Behavioral:</strong> agitation, aggression, verbal disruption, impulsivity</td>
<td></td>
</tr>
</tbody>
</table>

Tampi et al, Clinical Geriatrics, 2011
<table>
<thead>
<tr>
<th>Type of behaviors</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>21% to 60%</td>
</tr>
<tr>
<td>Apathy</td>
<td>48% to 92%</td>
</tr>
<tr>
<td>Delusions</td>
<td>16% to 70%</td>
</tr>
<tr>
<td>Depression</td>
<td>30% to 50%</td>
</tr>
<tr>
<td>Disinhibition/Impulsivity</td>
<td>30% to 35%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>4% to 76%</td>
</tr>
<tr>
<td>Inappropriate sexual behaviors</td>
<td>7% to 25%</td>
</tr>
<tr>
<td>Mood lability</td>
<td>30% to 40%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>20% to 25%</td>
</tr>
<tr>
<td>Stereotyped behaviors</td>
<td>12% to 84%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>15% to 20%</td>
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</tbody>
</table>

Tampi et al, Clinical Geriatrics, 2011
Impact of BPSD

- Diagnosis of dementia
- Indicates progression of illness
- Caregiver burden and burnout
- Placement at facilities
- Direct and indirect cost of care

Tampi et al, Clinical Geriatrics, 2011
Neurobiology

- Psychotic symptoms → Frontal, temporal, limbic cortices
- Apathy → Frontal lobes (Anterior cingulate gyrus)
- ApoE 3/4 homozygotes → Depression, anxiety, psychosis, agitation, sleep disorders
- Serotonin and Dopamine receptor polymorphisms → Psychosis and aggression

BPSD

- First degree relatives → Depression and psychosis
- Lower premorbid agreeableness

Tampi et al, Clinical Geriatrics, 2011
Evaluation and Management of Individuals with BPSD
Recognition is the first and the most important step in management

- Educate caregivers
- Assess and reverse aggravating factors, unmet needs
- Adapt to specific cognitive deficits
- Review and acknowledge the relevant losses or stressors
- Treatment should always be individualized
- Rule out and treat underlying medical conditions!
- Review neuropsychiatric diagnoses

Tampi et al, Clinical Geriatrics, 2011
Assessment

Obtain history
(Medical, Psychiatric, Medications, Pre-morbid personality, Cognition, Functions)
↓
Complete a physical examination
(Rule out underlying medical or neurological disorders)
↓
Order investigations
(Blood tests, Urine examination, Neuroimaging if indicated)
↓
Complete standardized rating scales and or neuropsychological testing
↓
Medical/Neurological disorders → Treat underlying disorder (s)
↓
Drug effect → Remove offending drug (s)
↓
Confirm BPSD

Tampi et al, Clinical Geriatrics, 2011
Non-Pharmacological

- Most effective
  - Psychoeducation
  - Instruction for caregivers/staff
  - Distraction/redirection

- Environmental considerations
  - Comfort (Pain? Need to toilet? Hungry? Thirsty?)
  - Change to routine/social interactions

Livingston et al, Am J Psychiatry, 2005
Livingston et al, B J Psychiatry, 2014
Non-Pharmacological

• May be effective
  – Cognitive stimulation therapy
  – Therapeutic activities
  – Specialized dementia units

• Others
  – Person-centered care, communication skills training
  – Activities and music therapy
  – Sensory interventions
    • Aromatherapy, light therapy
    • Massage

Livingston et al, Am J Psychiatry, 2005
Livingston et al, B J Psychiatry, 2014
Non-Pharmacological
Non-Pharmacological
Pharmacological

• Only for symptoms that persist even after the non-pharmacological steps have been undertaken

• Often a process of trial and error, weighing R/B

• Choice of medication may be influenced by the urgency of the situation

• Nothing is FDA-approved

Tampi et al, Clinical Geriatrics, 2011
Emergent behaviors

May need to be treated with medications i.e., antipsychotics or need inpatient psychiatric treatment

Non-emergent behaviors

Cluster the most salient features into patterns that is roughly analogous to a drug responsive syndrome

- Appears depressed: Use antidepressants
- Appears hypomanic/manic: Use mood stabilizers or antipsychotics
- Appears psychotic: Use antipsychotics

Tampi et al, Clinical Geriatrics, 2011
Select a medication class with some empirical evidence of efficacy and the highest likelihood of tolerability and safety.

The choice is often influenced by side effects, comorbidities, sx severity.

Start low and go slow.

Avoid polypharmacy if possible.

Frequently reassess target symptoms and monitor for toxicity (2-4 weeks).

Maintain for an appropriate period of time (4-12 weeks).

After the appropriate period (4-12 weeks), try to taper dose, i.e., the empirical trial in reverse.

Sometimes several medication trials are needed before the problem is ameliorated.

Tampi et al, Clinical Geriatric, 2011.
Typical Antipsychotics

• 11 RCTs, small sample sizes, 4-12 weeks duration
  – Modest advantage of typical antipsychotics over placebo
  – Significant improvement in aggression w/haloperidol
  – No improvement in other symptoms of agitation

• Adverse effects
  – Somnolence
  – EPS, TD
  – QTc prolongation
  – Black box warning

Ballard et al, Nat Rev Neurol, 2009
Atypical Antipsychotics

• Meta-analysis of 15 trials (2006)
  – Significant improvement in sx with aripiprazole and risperidone
  – Not for olanzapine and quetiapine
  – ~1/3 dropped out without differences between drug and placebo

• Adverse effects
  – Somnolence
  – EPS, TD
  – Cardiac, metabolic
  – Black box warning

Schneider et al, Am J Geriatr Psychiatry, 2006
**Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. CATIE: Dementia study**

<table>
<thead>
<tr>
<th>Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. CATIE: Dementia study</th>
<th>42-site, double-blind, placebo-controlled trial for 36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation</td>
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<tr>
<td><strong>Randomly assigned to receive:</strong></td>
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</tr>
<tr>
<td>Olanzapine (mean dose, 5.5 mg per day)</td>
<td></td>
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<tr>
<td>Quetiapine (mean dose, 56.5 mg per day)</td>
<td></td>
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<tr>
<td>Risperidone (mean dose, 1.0 mg per day)</td>
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<tr>
<td>Placebo</td>
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</table>

**The main outcomes were:**

1. The time from initial treatment to the **discontinuation of treatment** for any reason.

2. The number of patients with **at least minimal Improvement** on the **Clinical Global Impression of Change (CGIC)** scale at 12 weeks.
<table>
<thead>
<tr>
<th>Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. CATIE: Dementia study</th>
</tr>
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</table>

1. Time to the discontinuation of treatment for any reason:

- Olanzapine (median, 8.1 weeks)
- Quetiapine (median, 5.3 weeks)
- Risperidone (median, 7.4 weeks)
- Placebo (median, 8.0 weeks) \((P=0.52)\)

2. The median time to the discontinuation of treatment due to lack of efficacy:

- Olanzapine (22.1 weeks)
- Risperidone (26.7 weeks)
- Quetiapine (9.1 weeks)
- Placebo (9.0 weeks) \((P=0.002)\)

3. The following % of patients discontinued their assigned treatment owing to intolerability:

- 24% of patients who received olanzapine
- 16% of patients who received quetiapine
- 18% of patients who received risperidone
- 5% of patients who received placebo \((P=0.009)\)

4. Improvement on the CGIC scale. Improvement was observed in:

- 32% of patients assigned to olanzapine
- 26% of patients assigned to quetiapine
- 29% of patients assigned to risperidone
- 21% of patients assigned to placebo \((P=0.22)\)
## Cognitive Enhancer Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Rodda J, Morgan S, Walker Z. 2009 | Meta-analysis        | • 14 studies identified
• 9 donepezil, 3 galantamine and 2 rivastigmine
• Median study treatment length was 24 weeks
• 4 studies specifically designed to assess behavioral outcomes
• 3 studies found statistically significant but modest differences in NPI score between drug and placebo |
| Maidment ID, Fox CG, Boustani M, et al. 2008 | Meta-analysis        | • 6 randomized, parallel-group, double-blind studies
• 5/6 had NPI outcome data
• 868 patients on memantine & 882 patients on placebo
• Patients on memantine improved by 1.99 on the NPI scale compared to the placebo group |
# Mood Stabilizer Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study/Outcomes</th>
<th>Bottom-line</th>
</tr>
</thead>
</table>
| Lonergan E, Luxenberg J. 2009   | • Total of 3 RCTs<br>
• 2 were included in the meta-analysis                                           | • VPA ineffective<br>
• Valproate therapy is associated with an unacceptable rate of adverse effects |
| Konovalov S, Muralee S, Tampi RR. 2008 | • 7 RCTs: 2 CBZ, 5 VPA<br>
• 1 study: statistically significant improvement<br>
• 5 studies: no significant differences<br>
• 1 study: statistically significant worsening<br>
• More frequent adverse effects in the medication group | • Beneficial in some patients<br>
• Anticonvulsant mood stabilizers cannot be recommended for routine use in the treatment of BPSD at the present time |
| Kim Y, Wilkins KM, Tampi RR. 2008 | • 11 case reports, 3 case series and 1 retrospective chart review of Gabapentin<br>
• No controlled studies                                                           | • Well tolerated and effective treatment<br>
• Less well tolerated in patients with dementia with Lewy bodies                  |
# Antidepressant Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seitz DP, Adunuri N, Gill SS, et al. 2011</td>
<td>Meta-analysis</td>
<td>• 5 studies compared SSRIs to placebo, 2 combined in a meta-analysis&lt;br&gt;• In 2 studies sertraline and citalopram were associated with a reduction in symptoms of agitation&lt;br&gt;• No effect on trazodone compared to placebo and equal efficacy to haloperidol&lt;br&gt;• Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics</td>
</tr>
<tr>
<td>Henry G, Williamson D, Tampi RR. 2011</td>
<td>Literature review</td>
<td>• 19 placebo controlled trials&lt;br&gt;• 11 trials, 8 using a selective serotonin reuptake inhibitor (SSRI) compound and 3 using trazodone showed benefit in the treatment of BPSD&lt;br&gt;• The antidepressant drug was well tolerated in at least 14 of the 19 trials</td>
</tr>
</tbody>
</table>
Benzodiazepines: Systematic Review

Tampi RR, Tampi DJ. 2014

- Five RCTs.
- Most compare benzo to antipsychotic
- 4/5 studies: no significant difference in efficacy between the active drugs to treat the symptoms of BPSD
- There was no significant difference between the active drugs in terms of tolerability
- Available data, although limited, does not support the routine use of benzodiazepines for the treatment of BPSD
- Exceptions may include Lewy Body Dementia, sedation needed for procedures

• 6 published papers  

• All 3 RCTs identified some benefit for the use of analgesics in reducing BPSD  

• The analgesics appeared to be well tolerated in the included studies.  

• Major study limitations
  - Data exclusively from published RCTs  
  - English language publications  
  - No statistical methods used |

<table>
<thead>
<tr>
<th>Melatonin</th>
</tr>
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<tbody>
<tr>
<td>Improvement for melatonin compared with placebo in behavioral and affective symptoms:</td>
</tr>
<tr>
<td>Measured by the ADAS non-cognitive scale in a study of 20 patients</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory (NPI) following treatment with 2.5 mg/day melatonin but not with 10mg/day melatonin in a larger study of 157 patients</td>
</tr>
</tbody>
</table>

- 8 reports
- 117 individuals with a dementia (67 with AD, 8 with VD and 42 with unspecified dementia)
- 5 reports used dronabinol, 2 reports used THC and 1 study used nabilone (synthetic cannabinoid)
- 7 reports indicate symptomatic improvement
- Behaviors improved: agitation, aggression, impulsivity, nocturnal restlessness, wandering, and poor sleep
- 4/8 eight studies did not report any significant adverse effects
- Sedation most common AE, followed by delirium, urinary tract infection and confusion
Ensure optimization of cognitive sparing agents (cholinesterase inhibitor, memantine)

If agitation persists, try an SSRI

If SSRI fails, consider trazodone

If antidepressants fail, consider aripiprazole, risperidone or quetiapine

If those fail, consider olanzapine

If antipsychotics fail, consider divalproex or carbamazepine (with caution)

If monotherapy fails, only then consider combination therapy

Avoid benzos (usually)

Tampi et al, Clinical Geriatrics, 2011
Use antipsychotics when benefits > risks, discussion with caregivers (and document)

Start low, titrate to minimum effective dose

Educate caregivers on sx recurrence

In absence of chronic psych illness, no role for LAIs

In absence of delirium, haloperidol is not first line

When tapering, reassess monthly and for 4 months after d/c

If no response after 4 wks, taper and discontinue

Attempt taper and d/c within 4 months if sx are improved

APA Practice Guidelines
Recent controversies in the treatment of individuals with BPSD
FDA Black Box Warning

• 17 placebo controlled trials (Schneider et al 2005)
  – Involved olanzapine, aripiprazole, risperidone, or quetiapine
  – Enrolled a total of 5106 patients
  – 15 showed numerical increase in mortality (1.6-1.7 fold)

• Death was mainly due to heart related events or infections

• Warning extended to clozapine, ziprasidone and combination olanzapine, fluoxetine

• FDA subsequently added warning to FGAs
• Death occurred more often over the first 8-12 weeks of treatment

• Excess mortality not due to any particular atypical antipsychotic and it could only be appreciated when this class of medications were examined as a whole

• Subgroup analysis did not reveal differences between patients of lower cognitive function, psychosis of AD or inpatients versus outpatients

- A retrospective case-control study at VA

- 90,786 patients ≥ 65 years with a diagnosis of dementia

- A new prescription for an antipsychotic (haloperidol, olanzapine, quetiapine and risperidone), valproic acid and its derivatives or an antidepressant (46,008 medication users)

<table>
<thead>
<tr>
<th>Drug</th>
<th>% increased mortality</th>
<th>NNH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>3.8</td>
<td>26</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3.7</td>
<td>27</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5</td>
<td>40</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2.0</td>
<td>50</td>
<td>&lt; 0.01</td>
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</tbody>
</table>
Compared to antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>% increased mortality</th>
<th>NNH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>12.3</td>
<td>8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3.2</td>
<td>31</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Compared to quetiapine

<table>
<thead>
<tr>
<th>Drug</th>
<th>% increased mortality</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>1.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.5</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Antipsychotics: high dose vs. low dose, 3.5% greater mortality for high dose
Options for Treating Emergent Agitation

- Offer Risperidone: 0.25 mg-1.0 mg dose
- Or Aripiprazole 2.0-5.0 mg dose
- Or Quetiapine 25 mg-50 mg dose
- Or Olanzapine 2.5 mg-5 mg dose
- Can repeat dose in 0.5-1 hour if needed
- May need 1-2 repeats before the patient calms down.

- If patients is refusing PO medications and is very agitated or aggressive
  - Give IM Aripiprazole: 1.875 mg-7.5 mg dose
  - Or IM Olanzapine: 2.5 mg-5.0 mg dose
  - Or IM Haloperidol: 0.5 mg-2.0 mg dose
  - Can repeat dose in 0.5-1 hour if needed.
  - May need 1-2 repeats before the patient calms down.
  - Avoid Benzos (usually, exceptions as discussed)
Safety Considerations

- Family education (e.g., 911, inpatient psychiatry)
- Fall risk with psychotropics
- Access to firearms
- Substance use
- Elderly protective services, social work support
- Consult a colleague, “never worry alone”
References

References


• Tampi RR, Tampi DJ. Efficacy and Tolerability of Benzodiazepines for the Treatment of Behavioral and Psychological Symptoms of Dementia. A Systematic Review of Randomized Controlled Trials. Am J Alzheimers Dis Other Demen, Mar 06, 2014

Thank you!
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